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Convenient and efficient synthesis of Boc-/Z-/Fmoc-β-amino acids employing N-protected α-amino acid fluorides

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Abstract: A new and efficient method for the synthesis of N^{α}-Fmoc-/Boc-/Z-β-amino acids using the two-step Arndt-Eistert approach is described. Fmoc-/Boc-/Z-α-Amino acid fluorides were used for the acylation of diazomethane synthesizing Fmoc-/Boc-/Z-α-aminodiazoketones as crystalline solids with good yield and purity. They were then converted to the corresponding β-amino acids using PhCOOAg/dioxane/H_2O.

Abbreviations: DAST, (diethylamino)sulfur trifluoride; Fmoc, 9-fluorenylmthoxycarbonyl; HPLC, high-performance liquid chromatography; IR, infrared; RP, reverse phase; TFA, trifluoroacetic acid; TLC, thin-layer chromatography.

It is well-known that the Wolff rearrangement of diazoketones containing a chiral centre next to the carbonyl group occurs with retention of the configuration. This finding is the basis for the homologation of α-amino acids to β-amino acids using the Arndt-Eistert method (1, 2). The acylation of diazoalkanes using acid chlorides, or less commonly acid anhydrides, is a familiar procedure for the synthesis of α-diazoketones (3, 4). The requisite Boc- and Z-amino acid chlorides have limited shelf stability and decompose spontaneously to the corresponding Leuch's anhydrides. Consequently, the synthesis of Boc- and Z-α-aminodiazoketones involved the *in situ* treatment of the carboxylic acid with isobutyloxycarbonyl chloride or ethyl chloroformate to form the corresponding mixed anhydride, which was then allowed to react with diazomethane (5, 6). This route has been applied to the synthesis of several Boc-/Z-α-amino

acids. Although an equimolar quantity of a tertiary base has to be used during the mixed anhydride formation, the same method was also extended to the synthesis of Fmoc-α-aminodiazoketones (7). As the powerful activation present in acid chlorides is well known, Tos-α-aminodiazoketones were prepared starting from the corresponding acid chlorides (8). Unlike Boc-/Z-amino acid chlorides, Fmoc-amino acid chlorides are found to be shelf stable and racemization-free coupling agents. The acid chloride method was extended to the synthesis of several simple Fmoc-β-amino acids by Leggio *et al.* (9) and Gopi and Suresh Babu (unpublished results). Recently, we have found that the pentafluorophenyl ester method is suitable for the synthesis of Fmoc-β-amino acids (10).

β-Peptides are an emerging class of unnatural peptides with surprising secondary structural propensities. Seebach and colleagues (11–14), described helical and extended conformations adopted by short linear oligomers of acyclic β-amino acids. Gellman demonstrated that the homooligomers of *trans*-2-amino-cyclohexane and cyclopentane carboxylic acids form helical structures. Thus, the synthesis and characterization of β-peptides consisting of β-amino acids, is a field of research that has been receiving more and more interest in recent years (15, 16). In view of this, there is a need to develop an efficient and common route for the homologation of α-amino acids possesing Boc-/Z- and Fmoc groups to the corresponding β-amino acids. This paper describes the synthesis of N^{α}-protected β-amino acids using protected α-amino acid flourides as acylating agents (Fig. 1).

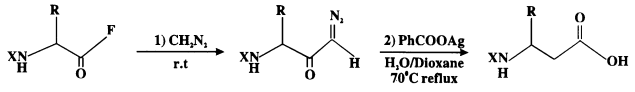
Results and Discussion

Acid fluorides of Boc- and Z-amino acids, similar to Fmoc-amino acids, are stable, crystalline and rapid-acting acylating agents (17, 18). They are stable in the case of amino acids bearing *t*-Bu, Boc or N-trityl side-chain protection. Other advantages include a greater stability towards water, including moisture in the air. The properties of Fmoc-amino acid fluorides have made them ideal candidates for both rapid solution and solid-phase synthesis. To sum up, these compounds are also an immediate choice for the synthesis of peptides containing highly hindered amino acids (19). The practical problems associated with the preparation of protected amino acid fluorides using cyanuric fluoride and tetramethylfluoroformamidinium hexafluorophosphate are circumvented by the use of (diethylamino)-sulfur trifluoride (DAST) as a fluorinating agent (20).

Diazomethane, generated using *N*-methyl-*N*-nitroso-toluene-*p*-sulfonamide (21), instead of *N*-methyl-*N*-nitrosourea, was passed into the cold CH_2Cl_2 solution containing protected amino acid fluoride and acylation reactions were carried out.

It has been found that the reaction of N-protected amino acid fluorides with diazomethane in CH_2Cl_2 proceeds smoothly within 15 min at room temperature. The acylation reaction with a sufficient excess of diazomethane results in complete conversion into the α-aminodiazoketone. The course of the reaction was monitored by thin-layer chromatography (TLC) using ethyl acetate/petroleum ether (1:1) or ethyl acetate/hexane (35:65) and the disappearence of the yellow colour can be observed. The resulting α-aminodiazoketones do not require any further purification. All the resulting Boc-/Z-/Fmoc-α-aminodiazoketone derivatives (Table 1, a–l) have been isolated as crystalline solids in 85–93% yield. The purity of the compounds was checked by high-performance liquid chromatography (HPLC). They were further characterized by infrared (IR) spectra [the characteristic band at 2100 cm^{-1} (COCH=NN group) and 1640 cm^{-1} (CO of $CHRCOCHN_2$)] and ^1H NMR. None of these data indicated the presence of the C-methyl esters of the starting compounds. The HPLC profiles of the crude reaction mixtures also revealed the same.

The resulting N^{α}-protected α-aminodiazoketones were then converted to the corresponding β-amino acids using Wolff rearrangement employing silver benzoate. All the β-amino acids (Table 2, a–l) were isolated as crystalline solids in 80–95% yield. The acylation of diazomethane, employing acid fluorides as acylating agents, was found to be free from racemization. This was determined by the ^{13}C NMR spectra of the Fmoc-Ile-DAM obtained using this method. The spectra was found to be similar to that reported by Leggio



I II III

X=Fmoc/Boc/Z

Compound No.	R	Compound No.	R
a	H	g	CH_3
b/c/j	C_6H_5	h	$CH(CH_3)_2$
d	CH_2COOBu^t	i	CH_2Ph
e	$CH_2CH_2COOBu^t$	k/l	$(CH_2)_2CH_3$
f	$CH(CH_3)CH_2CH_3$		

Figure 1. Synthesis of protected β-amino acids.

Table 1. **Fmoc-/Boc-/Z-α-aminodiazoketones**[a]

DAM derivative	Yield (%)	m.p. (°C)	$[\alpha]^{25}_{D}$ ($_{c\ 1,\ CHCl_3}$)	TLC RfA	RfC	IR (γ_{max}/cm^{-1})	^{1}H NMR
a Fmoc-Gly-DAM	93	110–112	–	0.60	0.86	3328, 2112	4.3 (3H, br); 4.59 (2H, d), 5.2 (1H, s), 5.41 (1H, br); 7.3–7.7 (8H, m)
						1714, 1636	
b Fmoc-Phg-DAM	90	148–149	–32.0	0.65	0.73	3416, 2107	4.25 (2H, m), 4.4 (2H, d), 5.1 (1H, s), 6.05 (1H, br), 7.2–7.8 (13H, m)
						1714, 1647	
c Fmoc-D-Phg-DAM	92	152–153	+32.3	0.69	0.84	3409, 2107	4.2 (2H, m), 4.5 (2H, d), 5.1 (1H, s), 6.05 (1H, br), 7.2–7.8 (13H, m)
						1702, 1647	
d Fmoc-Asp(OBu^t)-DAM	89	71–72	–26.3	0.80	0.84	3340, 2121	1.4 (9H, s), 2.0 (1H, m), 2.4 (2H, m), 4.3 (2H, d), 4.4–4.5 (2H, m),
						1688, 1647	5.4 (1H, s), 5.5 (1H, s), 7.8 (8H, m)
e Fmoc-Glu-(OBu^t)-DAM	85	137–138	–25.6	0.79	0.86	3328, 2112	1.44 (9H, s), 1.79 (1H, m), 2.1 (1H, m), 2.4 (2H, m), 4.2 (2H, d),
		(138.5–139.5)[7]	(–25.6)[7]			1720, 1643	4.3 (1H, br), 4.5 (1H, m), 5.4 (1H, s), 5.6 (1H, s), 7.8 (8H, m)
f Fmoc-Ile-DAM	94	143–144	–46.2	0.75	0.83	3302, 2105	0.93 (6H, d), 1.44 (2H, m), 1.84 (2H, m), 4.13 (1H, m), 4.42 (1H, m),
						1692, 1634	5.29 (1H, br), 5.35 (1H, br), 7.3–7.7 (8H, m)
g Boc-Ala-DAM	93	81–83	–21.0	0.71	0.82	3320, 2106	1.32 (9H, s), 4.21 (1H, m), 5.25 (1H, s), 5.5 (1H, br)
						1698, 1631	
h Boc-Val-DAM	94	61–62	–30.2	0.73	0.84	3339, 2107	0.92 (6H, d), 1.32 (9H, s), 1.75 (1H, m), 4.21 (1H, br), 5.20 (1H, s), 5.42 (1H, br)
						1698, 1636	
i Z-Phe-DAM	90	81–82	–42.0	0.65	0.82	3320, 2107	2.9 (2H, d), 4.5 (1H, m), 5.02 (2H, s), 5.14 (1H, s), 5.37 (1H, d), 7.2–7.8 (10H, m)
		(81–82.5)[5]	(–42.0)[5]			1700, 1636	
j Z-D-Phg-DAM	84	82–84	+36.2	0.69	0.75	3340, 2107	4.45 (1H, br), 5.0 (2H, s), 5.2 (1H, s), 5.4 (1H, br), 7.2–7.8 (10H, m)
						1714, 1647	
k Z-Nva-DAM	90	114–116	–33.2	0.66	0.79	3348, 2112	0.9–2.0[7H (m), 2.4 (1H, d), 3.75 (1H, m), 5.1 (1H, s), 5.6 (1H, br), 7.2 (5H, m)
						1714, 1636	
l Z-D-Nva-DAM	94	113–115	+33.4	0.68	0.73	3348, 2117	0.9–1.7 (7H, m), 2.5 (1H, d), 3.9 (1H, m), 5.01 (1H, s), 5.9 (1H, br), 7.2 (5H, m)
						1719, 1639	

a. All the compounds gave elemental analyses satisfactorily.

Table 2. **Fmoc-/Boc-/Z-β-amino acids**[a]

Fmoc-/Boc-/Z-β-amino acids	Yield (%)	m.p. (°C)	$[\alpha]_{(c\ 1,\ CHCl_3)}^{25}{}_D$	TLC R_fA	R_fC	IR (γ_{max}/cm^{-1})	^1H NMR
a Fmoc-β-HGly	90	148–150	–	0.61	0.78	3340, 1688	2.75 (2H, t), 3.46 (2H, m), 4.25 (1H, t), 4.59 (2H, d), 5.5 (1H, br), 7.2–7.8 (8H, m), 8.6 (1H, br)
b Fmoc-β-HPhg	85	96–98	– 22.0	0.65	0.70	3343, 1710	2.5 (2H, d), 4.25 (2H, m), 4.4 (2H, d), 5.85 (1H, br), 7.2–7.8 (13H, m), 8.3 (1H, br)
c Fmoc-β-D-HPhg	80	98–102	+21.8	0.68	0.69	3348, 1698	2.4 (2H, d), 4.25 (2H, m), 4.3 (2H, d), 5.80 (1H, br), 7.2–7.8 (13H, m), 8.3 (1H, br)
d Fmoc-β-HAsp(OBu^t)	80	82–83	+0.30	0.68	0.76	3329, 1703	1.43 (9H, s), 2.67 (4H, m), 4.2–4.4 (4H, m), 6.5 (1H, br), 7.2–7.8(8H, m)
e Fmoc-β-HGlu(OBu^t)	80	58–60 (58–60)[7]	– 11.4 (– 11.4)[7]	0.69	0.75	3430, 1720	1.4 (9H, s), 2.4 (4H, m), 3.8–4.4(4H, m), 5.6 (1H, d), 7.2–7.8 (8H, m)
f Fmoc-β-Ile	80	98–100	+16.8	0.65	0.62	3324, 1695	0.83 (6H, m), 1.34 (2H, m), 1.47 (4H, m), 2.31 (2H, m), 4.25 (2H, m), 7.2–7.8 (8H, m)
g Boc-β-HAla	92	98–99	– 18.0	0.62	0.58	3340, 1698	1.2 (3H, d), 1.33 [9H (s), 2.4 (2H, d), 4.01 (1H, m), 5.25 (1H, br), 8.4 (1H, br)
h Boc-β-HVal	90	65–66 (65–66)[22]	– 23.0 (– 23.4)[22]	0.57	0.56	3343, 1688	0.94 [6H (d), 1.32 (9H, s), 1.72 (1H, m), 2.5 (2H, d), 4.2 9(1H, br), 5.4 (1H, br), 8.3 (1H, br)
i Z-β-HPhe	86	84–85	– 36.0	0.67	0.60	3340, 1690	2.4 (2H, d), 4.2 (1H, m), 5.0 (2H, s), 5.3 (1H, br), 7.25 (10H, m).
j Z-β-HPhg	86	86–88	+18.3	0.69	0.62	3340, 1688	2.5 (2H, d), 4.2 (1H, m), 5.01 (2H, s), 5.46 (1H, b), 7.25 (10H,m).
k Z-β-HNva	80	82–83	– 29.1	0.67	0.63	3348, 1690	1.1–1.3 (7H, m), 2.6 (2H, d) 3.9 (1H, d), 5.8 (1H, br), 7.2 (5H, m).
l Z-β-D-HNva	82	83–85	+29.6	0.69	0.61	3346, 1692	1.2–1.5 (7H, m), 2.45 (2H, d), 3.8 (1H, d), 5.6 (1H, br), 7.2 (5H, m).

a. All the compounds gave elemental analyses satisfactorily.

et al. (9). Further, the comparison of the determined optical rotations of D- and L-isomers of Fmoc-Phg and those of the corresponding D- or L-β-Phg demonstrated that the Wolff rearrangement proceeds sterospecifically. Several of the other compounds had optical rotations similar to that reported earlier (Table 2).

Thus the synthesis of the optically pure and crystalline Boc-/Z-and Fmoc-α-aminodiazoketones can be synthesized by using N^{α}-protected α-amino acid fluorides as acylating agents. There is no need to use a base during acylation. This method is also applicable to the homologation of α-amino acids bearing *t*-butyl group side-chain protection.

Experimental

The melting points were determined using a Leitz-Wetzlar melting point apparatus and are uncorrected. Optical rotations were measured with an automatic AA-10 polarimeter (Optical Activity, UK). IR spectra were recorded on a Nicolet model Impact 400D FT-IR spectrometer (KBr pellets, 3 cm^{-1} resolution). ^1H NMR spectra were recorded on a Brucker ACF 200 MHz spectrometer using Me_4Si as an internal standard. Elemental analyses were recorded using a Perkin–Elmer Analyser and the samples were dried for 24 h under vacuum before analysis. Analytical reverse phase (RP)-HPLC was performed with a Waters LC-3000 system using a C-18 Bondapak column [3.9 × 300 mm 10 (spherical) using as the eluant acetonitrile – 0.1% trifluoroacetic acid (TFA) and H_2O (65:35; isocratic, flow rate; 0.7 mL/min, monitoring at 220 nm]. TLC analysis was carried out on precoated silica-gel plates using the following solvent systems: (i) $CHCl_3$/methanol/acetic acid (40:2:1, v/v/v); (ii) $CHCl_3$/methanol (9:1, v/v); and (iii) ethyl acetate/hexane (35:65, v/v) and R_f values are designated as R_fA R_fB and R_fC, respectively. The diazomethane (liquid dry diazomethane and its solution are explosives. Hence their preparation should be carried out only in a fume cupboard provided with a powerful exhaust system) solution in dry CH_2Cl_2 was prepared using *N*-methyl-*N*-nitroso-toluene-*p*-sulfonamide as reported previously (21). N-Fmoc-/Boc-/Z-α-amino acid fluorides were prepared using DAST (19, 20). To a stirred solution of Fmoc-/Boc-/Z-α-amino acid (1 mmol) in dry CH_2Cl_2 (10 mL), DAST (1.2 mmol, 0.13 mL) was added at room temperature. After 10 min, the mixture was extracted with ice water. The organic layer was separated, dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. Recrystallization using dichloromethane/*n*-hexane gave the acid fluoride as a crystalline solid. All protected amino acid fluorides were identified by IR. Several of the Boc-/Z-/Fmoc-α-amino acid fluorides were found to have the same physical constants as reported previously (17, 18).

Other derivatives prepared were: Z-Nva-F, m.p. 74–76°C; $[\alpha]^{D}_{25}$ + 11.2° (c = 1, $CHCl_3$); R_f C, 0.92; IR, 1678, 1848 cm^{-1}; Z-D-Nva-F, m.p., 78–79°C; $[\alpha]^{D}_{25}$–12.8° (c = 1, $CHCl_3$); R_f C, 0.91; IR, 1676, 1849 cm^{-1}.

II N-Fmoc-/Boc-/Z-α-aminodiazoketones: general procedure

Diazomethane gas was passed into an ice-cold solution of N-Fmoc-/Boc-/Z-α-amino acid fluoride (1 mmol) in anhydrous CH_2Cl_2 (40 mL) to saturation. The reaction mixture was stirred at room temperature for ≈ 15 min. Completion of the reaction was monitored by TLC. Excess diazomethane was decomposed by dropwise addition of acetic acid. The solvent was evaporated under reduced pressure and the resulting oily residue was precipitated using ethyl acetate/hexane and recrystallized using suitable solvents.

III N-Fmoc-/Boc-/Z-β-amino acids: general procedure

A solution of N-Fmoc-/Boc-/Z-α-aminodiazoketone (1 mmol) in 1,4-dioxane (10 mL) and water (5 mL) was treated with silver benzoate (5.7 mg, 2.5 × 10^{-2} mmol). The reaction mixture was refluxed at 70°C for 5 h and then filtered. The solvent was evaporated under reduced pressure. The residue was dissolved in saturated aqueous sodium carbonate (20 mL) and stirred for 30 min. The solution was washed with ether (2 × 30 mL). The aqueous layer was acidified to pH 2 and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with water (2 × 20 mL), dried over Na_2SO_4 and evaporated. The residue was precipitated using ethyl acetate/*n*-hexane to get the corresponding Fmoc-/Boc-/Z-β-amino acids in good yield.

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